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Citations and Editors' Notes

- GH Treatment in Non-GH-Deficient Indications
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The production of recombinant growth hormone (GH) in the mid-1980s and its use to replace GH-deficient adults in the 1990s has led to an explosion in our understanding of the hormones that regulate body composition. Over the next decade, it is likely that new growth factors and metabolic treatments will continue to expand our therapeutic options for treating patients with growth disorders.

Embracing new developments is essential in any medical specialty, but the growing volume of literature in the field of growth medicine places an increasing burden on healthcare professionals.

We are delighted to bring you the third issue in the new Current Medical Literature series Growth, Growth Hormone, and Metabolism, a review journal providing commentary and analysis on the most important advances in the field of growth medicine. Each issue of this journal presents specially commissioned review articles exploring issues of current and emerging clinical importance, in addition to a systematic review of the recent international literature.

The first Leading Article in this issue, by Marcia Bell and William Drake from St Bartholomew’s Hospital, London, UK, reviews the latest literature supporting individualized dose titration of GH during GH replacement in adult patients. In the second article, Heinz Zotter, from the Medical University of Graz, Austria, and colleagues discuss the recent literature concerning leptin responses to insulin administration in children with and without GH deficiency.

Future issues of the journal will explore a wide range of topics including the role of GH and insulin-like growth factor 1 (IGF-1) in the treatment of idiopathic short stature, IGF-1 treatment of Laron Dwarfism, and IGF and IGFBP-3 therapy for diabetes.

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Leading Article

Dose Titration of Growth Hormone in Growth Hormone Deficient Adults

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Growth hormone (GH) deficiency in adults has become a recognized clinical entity. The clinical syndrome is characterized by increased truncal and visceral fat, decreased lean body mass, decreased muscle strength, impaired exercise tolerance, and osteopenia [1–3]. It is associated with a lipid profile consistent with increased atherogenic risk, insulin resistance, altered cardiac structure and function, and reduced quality of life [4]. Adults with hypopituitarism are known to have an overall increased mortality rate [4–6]; it is possible that this may relate to untreated GH deficiency, although there is no direct evidence to support this at present. The availability of recombinant human GH (rhGH) has made the treatment of GH deficiency a reality, and many patients with symptomatic and biochemically severe GH deficiency are considered for GH replacement. Decreased serum levels of insulin-like growth factor 1 (IGF-1) and subnormal GH responses to stimuli, such as insulin-induced hypoglycemia, have been used as the gold standard for diagnosis of GH deficiency, and the Endocrine Society has recently published updated guidelines on how to best diagnose GH deficiency [7]. Attention is currently being focused on optimizing dosing schedules of rhGH in order to maximize its efficacy and minimize any potential adverse effects of therapy. Many experts in the management of pituitary disease believe that GH replacement is most effectively achieved by dose titration against a combination of serum markers of GH action such as IGF-1, measurements of clinical response, and tolerability [7–10]. The aim of this article is to review the latest literature supporting the individualized dose titration of GH during GH replacement in hypopituitary patients.

Dosing by weight
In the early studies of GH replacement in adults, the dose of GH adopted was extrapolated from that used in pediatric practice and was based on body weight or surface area [2,3,11,12]. The dose of rhGH replacement was adjusted if side effects occurred, and not in response to biochemical or clinical markers of GH action. As a result, many patients in these studies reported adverse events and had supraphysiological serum IGF-1 levels [6,13]. Side effects were more frequently reported in older patients and in those with a higher body mass index (BMI) [14]. It soon became apparent that the dose of GH needed to treat children and adolescents was far greater than that required to treat GH deficiency in adults, and as a result, lower doses of GH were used in later studies of adult GH deficiency [15–17].

Evidence suggests that spontaneous GH release correlates negatively with BMI and increasing age [18,19]. Carroll et al. compared high- and low-dose GH replacement regimens and found that lower weight-based doses of GH, sufficient to normalize serum IGF-1, resulted in similar improvements in waist:hip ratio and psychological well-being scores compared with higher doses [20]. Johannsson et al. demonstrated that baseline characteristics such as BMI, age, gender, and...
the level of GH binding protein were more important than the actual dose administered when determining an individual’s response to GH treatment [12]. Overall, dose regimens based on weight are now believed by many to be unphysiological and can result in excessive dosing, particularly in obese or older patients.

**Gender differences in response to GH**

Healthy, fertile females are known to secrete greater amounts of GH than aged-matched males [21–23], and GH deficient males are more responsive to rhGH therapy compared with females [24]. Several studies have also shown that oral, but not transdermal, estrogen replacement therapy results in relative GH resistance [25–27]. Conversely, androgen replacement has been shown to enhance IGF-1 generation [28], supporting the clinical concept that GH replacement in GH deficient patients should take these factors into account. Therefore, a weight-based dosing regimen is likely to result in relative GH under-replacement in females, particularly in those taking oral estrogen. Recently published guidelines by the Endocrine Society suggest that women who discontinue estrogen therapy, or who switch from oral to transdermal estrogen preparations, should have their maintenance dose of rhGH reduced [7]. Gender differences in response to GH replacement emphasize the need for individualized GH dose titration.

**Markers for GH replacement**

It is generally acknowledged that no precise marker of ideal GH replacement exists, and it is unlikely that GH replacement can be monitored adequately by clinical means alone. Potential biochemical markers of GH action include serum IGF-1, IGF binding protein-3 (IGFBP-3), the acid-labile subunit (ALS), and markers of bone turnover [29]. In order to be of use in assessing GH replacement, a biochemical marker of GH action must reflect the GH-deficient state [29]. Although low serum IGF-1 in an otherwise healthy individual is strongly suggestive of GH deficiency, a normal serum IGF-1 level does not rule out GH deficiency, particularly in older patients [29]. IGFBP-3 and ALS have been shown to correlate poorly with adult GH deficiency [30–32]; however, there is some evidence that IGFBP-3 is useful in determining GH deficiency in childhood [33], and correlates more closely with growth response than IGF-1 during therapy [34]. Markers of bone turnover are significantly increased in response to rhGH, but this response is highly variable and so far has found little use outside the clinical trials setting [35]. Serum IGF-1 is currently regarded as the most accurate biochemical marker of GH replacement in adults [29,32], but its production, in response to a given GH stimulus, is affected by many variables [36]. Clinically active acromegaly is known to be associated with supraphysiological IGF-1 levels [37]; however, symptoms of GH excess during rhGH replacement are not invariably associated with elevations of serum IGF-1 [29]. Therefore, in agreement with Johannsson [10] and others, the current authors believe that several markers of efficacy and safety should be measured during GH dose titration and maintenance to avoid the adverse effects of long-term treatment.

**GH titration regimen**

Drake et al. were the first to report an individualized rhGH titration regimen based on a defined target range of IGF-1 in a large patient cohort [8]. The investigators altered the rhGH dose to maintain serum IGF-1 between the median and upper limit of the age-related reference range. This target IGF-1 level was chosen in order to avoid the possible adverse effects associated with chronic exposure to supraphysiological IGF-1 levels, and to take into account the fact that a substantial proportion of adult-onset GH deficient patients have IGF-1 levels in the normal reference range. The group reported an overall reduction in dose requirements in the dose-titration group when compared with historical series where patients were treated with a weight-based regimen. There was a consequent reduction in the incidence of adverse events, with maintenance of efficacy,
Dose Titration of GH in GH Deficient Adults

as determined by favorable changes in body composition and general well-being. Female patients were found to require larger doses of rhGH to achieve the desired IGF-1 levels, and took longer to achieve a maintenance dose compared with their male counterparts (median 8 weeks in females vs. 4 weeks in males). It was therefore suggested that larger increments in dose during initial treatment would likely be appropriate in females. Simultaneous monitoring of IGFBP-3 and ALS in this study demonstrated their relative insensitivity to changes in GH doses. The group concluded that GH replacement could effectively be administered using a dose-titration regimen in order to achieve a good clinical response to treatment and avoid excess GH exposure.

Work by other groups endorses the use of a dose-titration regimen for GH replacement. Murray et al. used a dose-titration regimen aimed at normalizing serum IGF-1 in 65 adult patients with severe GH deficiency [9]. Although this group was unable to show any significant difference in metabolic parameters or body composition at baseline and following 8 months of GH replacement, they reported a significant improvement in quality of life, as reflected by improvements in two separate self-rating questionnaires used to assess quality of life (the Psychological General Well-Being Schedule [PGWB] and the Adult Growth Hormone Deficiency Assessment [AGHDA]). This study also showed that the degree of improvement in quality of life was dependent on the level of quality-of-life impairment before GH was commenced. The group did not comment on the incidence of adverse events in the study population.

Johannsson et al. compared weight-based rhGH dosing with an individualized dose titration approach that was independent of body weight [10]. In this study, dose adjustments in the individualized dosing group were guided by clinical response and measurements of body composition, and normalization of serum IGF-1 levels. When adjusting the rhGH dose in the dose-titration group, priority was given to the factor that demonstrated the greatest deviation from normal. Both study groups showed similar responses to treatment with respect to body composition and to the majority of metabolic parameters, with significantly fewer side effects seen in the dose-titration group. The final dose of GH in the weight-based dosing group was significantly higher compared with that of the dose-titration group. It was also found that women were given more GH per body weight than men, and older patients were given significantly less GH per body weight than younger patients. Serum IGF-1 was higher in the weight-based group throughout the study period, but was also elevated above the reference range in approximately 20% of patients in the dose titration group as a result of dose increments being made in some of this group on the basis of persistently abnormal body composition. This observation highlights individual responsiveness to rhGH therapy and outlines the importance of carefully monitoring GH replacement by various modalities in a setting where no ideal marker for response to treatment exists.

More recently, the results of a large international, randomized controlled trial comparing a weight-based rhGH dosing regimen with an individualized dosing regimen were reported [38]. GH dose was titrated against clinical response and serum IGF-1. The investigators showed that an individualized dosing regimen had similar efficacy, but greater tolerability than a weight-based regimen. When both groups were compared, the patients in the dose-titration group received a significantly lower final dose of rhGH than those in the weight-based group.

Overall, data from these studies using individualized dose-titration regimens have shown that women were given more GH per kg of body weight compared with men, and older patients who were given less GH per kg of body weight, than those who were younger. This reflects the normal physiology of GH secretion in healthy adults [18,21–23]. Individualized regimens have consistently shown a reduction in the overall rhGH dose.
required in order to normalize serum IGF-1 levels and achieve a similar clinical response. Adverse events also occurred less frequently in the dose titration groups.

**Neoplasia in hypopituitary patients**

Concerns exist about the risk of neoplasia in hypopituitary patients receiving long-term GH treatment. Experience from long-term surveillance studies of pediatric patients is reassuring, with no published evidence to date of an increased risk of new or recurrent tumor growth. GH deficiency occurring in adulthood is predominantly due to pituitary or peripituitary tumors and their associated therapy, and the risk of recurrence of these tumors on GH replacement has been raised. Recent studies have, however, suggested that rhGH replacement does not cause a recurrence of pituitary or peripituitary tumors. An observational study by Frajese et al. of 100 patients with adult-onset GH deficiency treated with rhGH using dose titration against serum IGF-1 reported no obvious increase in the rate of hypothalamo-pituitary tumor recurrence [39]. It is of interest to note that 91% of patients in this series had received pituitary radiotherapy. Chung et al. also reported safety data on 50 patients with non-anterior pituitary parasellar tumors treated with GH by dose titration who underwent rigorous surveillance imaging [40]. Again, 70% of this patient group had received pituitary radiotherapy as part of the original management of their tumor. Both of these studies also provide data that supports the safety and efficacy of the rhGH dose-titration regimen [39,40].

**Treatment of GH deficiency**

Determining which patients with GH deficiency will benefit most from GH replacement is difficult. However, it is clear that this decision needs to be made on an individual patient basis, and at present rhGH replacement is usually offered to those patients with significant clinical manifestations of GH deficiency syndrome and biochemically proven severe GH deficiency [7]. In adult patients with hypopituitarism it is important to optimize anterior pituitary therapy prior to commencing GH treatment. Treatment of GH deficient adults with rhGH is known to improve body composition, lipid profiles, and quality of life, but it is not known whether long-term rhGH therapy restores life expectancy to normal in adult hypopituitary patients. Against this background, it is essential that GH replacement protocols minimize any potential adverse effects of therapy; thus, patients on life-long GH replacement require careful follow-up. In the current authors’ unit, among others, it has become routine to image the hypothalamo-pituitary region immediately before commencing GH replacement and at regular intervals thereafter. GH replacement is most appropriately commenced at a low starting dose and titrated according to clinical response, and age- and sex- adjusted values for serum IGF-1. There is a growing body of evidence to support the safety and efficacy of individualized dose titration of GH therapy, such that recent experience in adult clinical practice is likely to result in a degree of re-evaluation of traditional weight and surface area-based dosing in the pediatric setting [36].

References


Leading Article

Effect of Standard Insulin Tolerance Test on Plasma Leptin Levels in Children with and without Growth Hormone Deficiency

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Leptin is an adipocyte-derived hormone that enhances satiety and reduces food intake, and is involved in the maintenance of energy balance and body weight [1–4]. In humans, plasma leptin concentration is strongly correlated to the amount of body fat and body mass index [3–7].

The discovery of the obese gene and leptin [2] has provided a relevant clue to the understanding of interactions between hypothalamic regions that control food intake and peripheral energy stores [8,9]. It has been postulated that insulin induces obese gene expression in vivo in rats and in fat cell cultures [10,11]. Moreover, in adults it has been shown that insulin stimulation produces modifications of plasma leptin levels [12,13].

Studies describing leptin responses to hyperinsulinemia have been conflicting, with reports of both an increase and a decrease of plasma leptin levels. Therefore, it was the aim of this article to review the literature concerning leptin responses to insulin administration in children born with short stature.

Methods
In order to find the literature, a PubMed search was carried out using the following keywords: leptin, insulin, hyperinsulinemia, hypoglycemia, hyperglycemia, euglycemia, children, short stature, growth hormone, and idiopathic short stature.

The studies are discussed, with special regard to children with and without growth hormone (GH) deficiency.

Discussion
Since the discovery of leptin, the understanding of its physiological role has evolved from a satiety signal to that of an integrative hormone that responds to, and regulates, different endocrine pathways, with direct metabolic effects on peripheral tissues [4,7,9,14]. Leptin plays an integral role in energy homeostasis and may even be important during stress [15]. Although it is evident that caloric deprivation decreases plasma leptin levels [16,17], responses of the hormone during repeated episodes of physiological stress, such as hypoglycemia, remain undetermined. A confounding variable when studying the impact of hypoglycemia on plasma leptin levels is that experimental hypoglycemia may cause both an increase and a decrease in plasma leptin levels in adults [18–21].

Recently, the current authors have shown that insulin administration in children with short stature decreases plasma leptin levels 60 and 120 min after intravenous insulin injection [18]. In this study, this effect was independent of GH deficiency. Furthermore, no statistically significant difference was found in plasma leptin levels before insulin administration, 1 h and 2 h thereafter, or in percentage leptin decrease (in percentage)
when comparing patients with GH deficiency and children with idiopathic short stature [18]. Concerning the effect of insulin administration on plasma leptin levels, it is essential to take into consideration whether hyperinsulinemia is accompanied by hypoglycemia. Whereas in the above study glucose levels fell below a defined hypoglycemia threshold of 2.2 mmol/L in all subjects (with a nadir of 1.4±0.1 mmol/L) [18], other studies have shown that prolonged elevations of insulin under euglycemic conditions may increase plasma leptin levels [19–21]. It has been demonstrated that a 6-h hyperinsulinemic euglycemic clamp caused a 147±7% increase over baseline in plasma leptin levels in healthy lean males, but 6 h of hyperinsulinemia with graded hypoglycemia blunted the increase in plasma leptin levels [20]. In response to hypoglycemia, plasma leptin levels decreased in healthy adults, but not in patients with insulin-dependent diabetes [17]. Wellhoener et al. exposed subjects to four different conditions: high insulin, with either euglycemia or graded hypoglycemia, and low insulin, with either euglycemia or graded hypoglycemia [21]. With both high and low insulin levels, the insulin-induced increase in plasma leptin levels was attenuated by 50% during hypoglycemia [21]. Thus, hypoglycemia counteracts the stimulatory effect of hyperinsulinemia on plasma leptin levels. The evidence that hypoglycemia induced by hyperinsulinemia inhibits rises in plasma leptin levels, supports the hypothesis that low glucose levels during a prolonged fast, directly or indirectly, signal the adipocyte to reduce leptin secretion [17].

It is well established that changes in leptin have marked effects on metabolism. Increases in leptin can elevate hepatic glucose production in rats in the post-absorptive state [22]. Reports also demonstrate leptin-induced fat mobilization and fatty acid oxidation in mice [23]. Therefore, a major function of leptin may be to switch fuel utilization from carbohydrates to fat [24,25]. This metabolic impact could be important during hypoglycemia, where leptin decrease could contribute to a shift towards carbohydrate utilization, allowing quicker generation of ATP [17].

Leptin levels have been shown to be inversely related to pituitary–adrenal function [26]. In adults and in children with short stature, no obvious differences between patients with and without GH deficiency were found [18,26]. This indicates that GH has no direct effect on short-term leptin regulation, as found by others [27,28]. Although it has also been reported that in adults with GH deficiency there was no difference in leptin levels when adjusted for body mass index and gender compared with healthy subjects [29], in adolescents with GH deficiency, GH treatment caused a substantial increase in the nocturnal leptin peak during the second night after commencing substitution [30,31]. Whether this effect was due to an increase in insulin or directly caused by GH remains unclear. In children with isolated GH deficiency, leptin levels were normal before therapy and decreased after 4 weeks of GH therapy, which could not be explained by changes in body composition [32]. In vitro, GH led to a moderate reduction in leptin release from human adipocytes. This inhibitory effect was only observed in the presence of insulin, suggesting that GH interacts with the stimulatory effect of insulin [33].

Summary
A confounding variable when studying the impact of insulin on plasma leptin levels is that experimental hyperinsulinemia may cause both an increase and a decrease in plasma leptin levels in humans. Therefore, it was the aim of the present study to review the literature concerning leptin responses to insulin administration in children born with short stature.

For this purpose, a PubMed search was carried out and the literature was discussed, with special regard to children with and without GH deficiency.

In summary, the literature indicates that insulin administration may increase and decrease plasma leptin levels in humans depending on the presence of hypoglycemia.
In children with short stature, a standard insulin tolerance test that is accompanied by hypoglycemia leads to a decrease in plasma leptin levels in those with and without GH deficiency.

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References

Aortic distensibility and dimensions and the effects of growth hormone treatment in the turner syndrome.

Editor’s note: There has been concern that growth hormone (GH) treatment for non-GH-deficient indications might be associated with a variety of physical and long-term metabolic consequences. Such consequences might be difficult to identify in short-term studies and will naturally require long-term surveillance of patients in these cohorts. A problem facing researchers conducting long-term studies is the recruitment of untreated control patients to match with treated patients, particularly as more individuals with disorders eligible for GH treatment are attracted to that option for management.

Turner syndrome (TS) poses a particular investigative and management dilemma, as cardiovascular anatomical (structural) and functional (e.g. hypertension) problems have been under-evaluated in the past. However, improved research resources and imaging techniques indicate that structural cardiovascular malformations are present in ≤76% of patients with TS.

The present authors compared 38 TS women who received GH treatment at a variety of doses during childhood with 27 TS women who did not receive GH treatment. Four aortic dimensions and distensibility were assessed using magnetic resonance imaging:

• The ascending aorta.
• The descending aorta.
• The level of the diaphragm.
• The abdominal aorta.

TS patients had larger aortic diameters and reduced aortic distensibility compared with controls. In general, GH treatment increased distensibility except in TS patients who received the lowest dose of GH, who had larger aortic diameters and reduced distensibility compared with control subjects.

These findings do not meet with theoretical expectations, and it may be that individual patients have followed a natural progression of their aortic anatomy with age, independent of GH treatment, and thus confounded the observations. In other groups of children treated with GH (e.g. for congenital heart disease with short stature or Noonan syndrome), no adverse effects of GH treatment have been observed on cardiac size and function. Thus, the adolescent with TS is clearly an important focus for cardiovascular assessment.

Inflammatory markers in adults with Prader-Willi syndrome before and during 12 months growth hormone treatment.

Editor’s note: Growth hormone (GH) treatment for patients with Prader–Willi syndrome (PWS) is primarily licensed for children on the basis of its ability to reduce fat mass when used in association with an
appropriate calorie-constrained diet. The majority of PWS patients are believed to be functionally GH deficient to some degree. This idea is partly supported by the improved linear growth that is observed in response to treatment. Thus, the long-term morbidity due to cardiovascular disorders found in adult PWS patients may not simply be a result of obesity and obstructive respiratory disorders, but may be exacerbated by partial GH deficiency.

The present study sought to define whether or not PWS adults show abnormal levels of the inflammatory markers interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), high sensitive C-reactive protein (HCRP), and cholesterol, triglycerides, leptin, adiponectin, and glucose and insulin status levels associated with obesity and GH deficiency. Body fat levels were determined by dual X-ray absorptiometry. The authors recruited 12 PWS adults, aged 17–37 years, with a median body mass index of 34 kg/m² (range 21–50 kg/m²). The patients were assessed at baseline and after 6 and 12 months of GH treatment, which was dose titrated to keep serum insulin-like growth factor-1 (IGF-1) within the normal age-related reference range. Daily calorie intake was continued at 1000 kcal/day, which had been maintained for several years in these patients using a strict diet.

Baseline leptin levels were appropriate for individual degrees of adiposity, one patient had overt diabetes and half of the patients had insulin resistance (calculated using the homeostasis model assessment index). Four patients were hypertensive and receiving appropriate antihypertensive agents, and eight patients were hypogonadal. These varied clinical circumstances may have impacted in different ways on the observed inflammatory markers. However, baseline IL-6 was elevated in nine patients, HCRP elevated in seven patients, and TNF-α levels were within the normal range in all patients. After 12 months of GH treatment, median IGF-1 levels increased approximately two-fold, median body fat was reduced by 10%, and median lean body mass increased by 20% (p<0.05). GH treatment was associated with a non-significant reduction in IL-6 and HCRP levels for the whole group at both 6 and 12 months. Notably, the diabetic patient was able to stop treatment for diabetes after starting GH treatment.

This small study clearly needs to be expanded with a larger cohort of patients to disentangle the many clinical variables that might influence inflammatory marker profiles, and show possible situations in which GH treatment may have a therapeutic role.

Self-esteem and social adjustment in young women with Turner syndrome - influence of pubertal management and sexuality: population-based cohort study.

Editor's note: This remarkable study reports the evaluation of the impact of pubertal management (timing of induction) on 566 French adult women with Turner syndrome (TS). Throughout childhood and adolescence, data regarding TS, growth, and treatment were collected, and at a mean age of 22 years (range 18–31) the studied TS patients were invited to complete a questionnaire. The survey included:

• The Cooperman’s Self-Esteem Inventory (SEI).
• The Social Adjustment Scale Self-Report (SAS-SR).
• Short Form 36 (SF-36) of the Medical Outcome Study.
• The General Health Questionnaire 12 (GHQ-12), which measures psychological distress.

Patients also answered questions regarding demographic characteristics, sexual experience, current health status, and expectations from growth hormone (GH) treatment.

The most important observations from a life-style perspective were that a low self-esteem was associated with limited sexual experience, with impaired auditory function, and with persistent otological abnormalities.
Auditory and otological problems have become increasingly apparent in recent years in adult women with TS. In addition, low social adjustment was associated with low paternal socio-economic class. Late age at first kiss was associated with late induction of puberty, which in itself might be related through medical management as being a causal association with cardiac disorders. Not surprisingly, age at first sexual intercourse was related to age at puberty, and delayed induction of puberty had “a long-lasting effect on sex life”. However, the finding most relevant to growth management was that final adult height and height gain due to GH had no effect on psychological outcomes, and the authors question the value of GH treatment in TS patients.

Pegvisomant for the treatment of gsp-mediated growth hormone excess in patients with McCune-Albright syndrome.

Editor’s note: Hypersecretion of growth hormone (GH) may occur in approximately 20% of patients with McCune–Albright syndrome (MAS), arising in childhood or developing later in life. A proportion of these patients will have identifiable pituitary adenomas, whereas others may have more generalized somatotrophic hypersecretion without tumor. Many have coexistent polyostotic fibrous dysplasia (PFD), which, when affecting the skull bones, will render trans-sphenoidal surgery impractical. Pituitary irradiation is contra-indicated because of a predisposition of PFD to undergo sarcomatous transformation. Long-term medical therapy with somatostatin (or analogue), with or without dopamine receptor agonists, has hitherto been the treatment of preference in these thankfully rare cases. The development of the GH receptor antagonist “pegvisomant” offers a similar opportunity for control in such MAS patients as has been shown in recent years for symptomatic control of GH excess in acromegaly resistant to other treatment options.

This randomized, double-blinded, placebo-controlled crossover study of five MAS patients aged 13–39 years was comprised of:

• An initial 12-week washout period, in which GH excess treatments were discontinued.
• A first 12-week treatment period, in which patients received 20 mg/day pegvisomant or a placebo, administered subcutaneously.
• A 6-week washout period.
• A second 12-week treatment course, in which pegvisomant and placebo regimens were crossed-over.

The recruited patients had GH that did not suppress below 1 ng/mL on a standard oral glucose test. The primary measure of drug efficacy was normalization of serum insulin-like growth factor-1 (IGF-1) to age-specific and gender-specific references, and this was successfully achieved by 6 weeks in four of the patients when treated with pegvisomant. The other patient was subsequently controlled with a combination of lanreotide and pegvisomant. In addition, a more modest reduction in IGF binding protein-3 was achieved, without change in random serum GH levels. Pituitary magnetic resonance imaging showed no evidence of increased pituitary volume from baseline to 12 months for the cohort as a whole, although one patient did show an increase in pituitary volume (clinical significance not reported). A standard panel of bone metabolism markers showed no change during pegvisomant treatment and there was no overall change in subjective, reported bone pain (scored on a weekly basis throughout the study). This suggests that there was no positive or negative effect of pegvisomant on PFD. Interestingly, pegvisomant had no effect on symptoms of fatigue and sweating, possibly because the authors targeted IGF-1 suppression as the endpoint rather than titrating pegvisomant dose to symptoms removal. Whilst pegvisomant is clearly effective in MAS-associated GH excess, factors such as cost and optimal injection frequency will determine clinical utility.
New growth factor therapies aimed at improving intestinal adaptation in short bowel syndrome.

Pereira PM, Bines JE.
Royal Children's Hospital, Melbourne, VIC, Australia.

Editor's note: There has been extensive animal-based research over the last 15 years evaluating the role of a variety of growth factors as trophic agents. They may have clinical applications in adaptive recovery or treatment for malabsorption and malnutrition resulting from massive small bowel resection due to a variety of congenital intestinal disorders and acquired conditions. The most likely candidates for treatment of short bowel syndrome (SBS) at present are growth hormone (GH), glucagon-like peptide-2 (GLP-2), epidermal growth factor (EGF), and insulin-like growth factor-1 (IGF-1) and its binding proteins or analogues.

The present review provides a concise update on the progress to date within this field, and highlights the lack of data within clinical settings due to the relative rarity of SBS. The role of GH in pediatric cases is summarized by considering just five patients in three case studies. If significant progress is to be made at clinical level then careful multicenter trials with appropriate protocols and outcome measures are clearly essential for any single agent or combined treatments.

[1] Milk as a food for growth?
The insulin-like growth factors link.
Rogers I, Emmett P, Gunnell D et al.
University of Bristol, Bristol, UK.

Sandhu J, Davey Smith G, Holly J et al.
University of Bristol, Bristol, UK.

Editor's note: These two papers are linked by common interests within Bristol-based units (UK) that focus on the dietary determinants of serum insulin-like growth factor-1 (IGF-1) and its relationship with IGF binding protein 3 (IGFBP-3) and childhood growth, and the potential association of higher (free) IGF-1 levels with certain types of cancer in late life.

The first study found an association between leg length, IGF-1, IGFBP-3, and cancer risk, and the authors attributed this to the milk protein content of diet [1]. However, dairy product intake was correlated with increased leg length in boys, but with decreased leg length in girls.

In females, early onset of puberty and its association with tall stature, constitutional advanced development, and earlier estrogen exposure has been clearly linked with increased risk of breast cancer. However, the second study, unusually, focused on males, for whom good retrospective data on pubertal timing were available [2]. Age at peak height velocity (APHV) in puberty was inversely associated with adult IGF-1 levels and body mass index (BMI), as were prepubertal childhood height and BMI. In contrast, APHV was positively associated with adult height.

Does long-term GH replacement therapy in hypopituitary adults with GH deficiency normalise quality of life?
Koltowska-Haggstrom M, Mattsson AF, Monson JP et al.
Pfizer, Sollentuna, Sweden.

Editor's note: Impairment of quality of life (QoL) in adult patients with growth hormone (GH) deficiency caused by hypopituitarism is a well-recognized phenomenon that was first reported over 40 years ago. Whilst many studies have confirmed this impairment, the benefit of recombinant human GH (rhGH) replacement therapy on QoL measures remains contentious, with recent clinical trials producing conflicting results. This may be because the studies concerned have tended to be quite small in size, and have not compared the impact of rhGH therapy on
QoL with normative data obtained from local reference populations.

In this report, the large Kabi International Metabolic Study (KIMS) database is utilized and QoL data obtained for those all those patients (n=1686) registered in four participating European countries. These data were compared with QoL data taken from corresponding general population samples for each country (England & Wales n=892, The Netherlands n=1038, Spain n=868, and Sweden n=1682). Change in total QoL scores and responses to treatment (using 4–6 years follow-up data) were evaluated, and revealed that long-term rhGH replacement therapy in GH deficient adults improved QoL to nearly country-specific normative levels. This was especially evident during the first 12 months of treatment, with a steady and gradual improvement over time until the general population reference range was reached. Problems with memory and tiredness were the most debilitating symptoms for patients prior to starting rhGH therapy, followed by problems with tenseness, self-confidence, and difficulties with socialization. Interestingly, treatment with rhGH improved all these problems in reverse order, a novel observation that was consistent across the four countries. Furthermore, the degree of baseline impairment in QoL did not appear to determine the extent of sustained and lasting improvement in QoL, or the observed pattern of treatment response. In conclusion, the authors suggested that the results supported the hypothesis that GH deficiency alone might be the direct cause for the psychological problems experienced by many GH deficient patients.

In vivo imaging of hepatic growth hormone signaling.

Frank SJ, Wang X, He K et al.
University of Alabama at Birmingham, Birmingham, AL, USA.

Editor’s note: The development of novel, non-invasive experimental techniques that do not involve the use of animals or the harvesting of tissue samples may be the next step in studying the physiology of hormone action in vivo. Using adenoviral-mediated gene delivery systems in combination with sensitive, non-invasive imaging on animal experimental models may offer a number of advantages, including the ability to perform serial measurements or experiments within the same animal. This would allow more relevant biological endpoints of hormone action to be determined.

The present paper reports on the development of a novel, non-invasive bioluminescence technique for the imaging and assessment of in vivo hepatic growth hormone (GH) action. Taking advantage of the new gene delivery systems and imaging techniques, the authors coupled a signal transducer and activation of transcription-5B (STAT-5B)-dependent GH response element to a luciferase reporter. STAT-5-driven transcriptional activation of the fused upstream coding region for firefly luciferase enabled measurement of light emission in response to GH.

The GH–luciferase response element was incorporated into an adenoviral vector and injected into female nude mice, GH was administered exogenously, and the in vivo effects of hepatic GH signaling were studied. Luminescence responses in the region of the liver were detected by gamma camera, and were evident within 1 h of GH injection, peaking after 3 h. The dose–response effects of GH administration were also tested, and statistically significant dose-dependent effects of GH were observed in liver luciferase signal following GH injection, confirming that the ability of this system to detect graded responses. Subsequently, similar patterns of GH dose-dependent responsiveness were observed when the GH injection experiments were repeated on four other occasions over a 10-day period in the same mice. Experiments in which there was co-administration of GH receptor with GH significantly enhanced the GH responses as detected using bioluminescence.

The preliminary work presented in this paper potentially heralds a new era of in vivo hormone study, and the technique described may serve as an important blueprint for
non-invasive and repeated studies of the effects of hormone signaling via receptors expressed in the liver and in other tissues.

Sleep apnoea and quality of life in growth hormone (GH)-deficient adults before and after 6 months of GH replacement therapy.

Peker Y, Svensson J, Hedner J et al. Skaraborg Hospital, Skoevde, Sweden.

Clin Endocrinol (Oxf) 2006;65:98–105.

Editor’s note: Growth hormone (GH) is known to have complex effects on sleep by acting on the central nervous system and the upper airways, affecting both sleep quality and breathing patterns. In patients with untreated acromegaly, and thus GH excess, obstructive sleep apnea (OSA) is frequently observed. Therefore, concerns have been raised that recombinant human GH (rhGH) replacement therapy may induce OSA and other disturbances in sleep architecture in GH deficient patients.

Peker and colleagues report what appears to be the first prospective observational study of a small cohort of GH deficient adult subjects (n=19, mean age of 53 years). Detailed polysomnographic and quality of life assessments (including electroencephalogram, electromyography, electrocardiogram, electro-oculography, body position detector, and respiratory monitoring) were conducted before and immediately after 6 months of daily treatment with rhGH. Treatment with rhGH (dose range 0.14–0.33 mg/day) was not associated with a significant change in mean total sleep time, or the proportions of slow wave sleep (SWS) and rapid eye movement (REM) sleep. It is noteworthy that 12/19 subjects had evidence of OSA at baseline, before the onset of rhGH therapy. This was associated with having a higher body mass index, waist:hip ratio, and age. Subjects with OSA at baseline had evidence of less SWS and REM sleep compared with the remaining seven subjects without OSA at baseline. The OSA symptoms were significantly improved with rhGH therapy.

Although this was a small study, the results challenge suggestions that rhGH therapy may induce OSA in GH deficient patients. In contrast, OSA may be present before the onset of therapy. Thus, the authors concluded that OSA should not be a major concern if appropriate rhGH therapy is performed, and may indeed benefit overall sleep quality.

The d3/GH receptor polymorphism does not influence the effect of GH treatment (66 μg/kg/day) or the spontaneous growth in short non-GH-deficient small-for-gestational-age children: results from a two-year controlled prospective study in 170 Spanish patients.


Editor’s note: The d3 growth hormone receptor gene (d3-GHR) polymorphism has recently been the focus of much attention, with a number of research groups reporting significant relationships between d3-GHR genotype and responsiveness to GH therapy. These relationships have been observed in GH deficient patients, Turner syndrome patients, and small-for-gestational-age (SGA) patients, but have not been consistently observed in different categories of recombinant human GH (rhGH) treatment recipients.

In a 2-year, prospective, randomized controlled trial of rhGH therapy for children with short stature attributed to SGA, 86 subjects received treatment (mean dose 66 μg/kg/day) whilst 84 untreated subjects served as controls. Genotypic frequencies for the three d3-GHR genotypes (d3/d3; d3/fl; fl/fl) were determined for the entire cohort, and data pertinent to growth were recorded and analyzed. Data regarding patients who remained prepubertal during the study (group 1: 68 GH-treated, 72 non-GH-treated), were compared with data for the entire cohort (group 2).

As expected, height velocity and height standard deviation for stature (SDS) increased in the rhGH-treated children, but not in the non-rhGH-treated controls. In both untreated and treated groups, height
velocity, change in height SDS, and other auxological parameters did not differ between the three d3-GHR genotypes. Furthermore, there was no correlation between genotype and pubertal status during the study.

These results are at odds with an earlier study in children receiving rhGH (30 μg/kg/day) for SGA, in which d3-GHR genotype significantly determined rhGH therapy responsiveness. Patients with d3/d3 and d3/fl genotypes grew more compared with the fl/fl genotype patients (Nat Genet 2004;36:720–24). The authors of the present paper speculated that the use of higher doses of rhGH in their study might explain the different results in the two studies. However, although the authors add to the d3-GHR literature, they fail to answer the question as to whether or not the d3-GHR polymorphism has an effect on growth rate response to GH therapy.

**IGFBP-1 involvement in intra-uterine growth retardation: study on IGFBP-1 overexpressing transgenic mice.**

Editor’s note: Gene targeting studies have conclusively shown that both insulin-like growth factor-1 (IGF-1), IGF-2, their receptors, and their binding proteins (IGFBPs) are important determinants of both prenatal and post-natal growth. It is also recognized that the IGF system has important effects on bone growth and development, although the endocrine role of IGFBP-1 in regulating this process has not been specifically studied to date.

In the present study, the endocrine effects of IGFBP-1 on fetal bone development and on carbohydrate metabolism were studied using a transgenic mouse model that over-expressed human IGFBP-1. Homozygous mice for IGFBP-1 over-expression had evidence of growth restriction from embryonic day (E) 17.5, and had a birth weight 20% lower than non-transgenic mice. Furthermore, homozygous mice exhibited delays in bone mineralization and defects in cartilage formation that persisted into early post-natal life. Hepatic glycogen stores were significantly lower in homozygous mice during fetal life compared with non-transgenic mice. This lower energetic reservoir was also found in the homozygous newborn animals, together with lower mean blood glucose levels (1.9 mM in homozygous mice vs. 3.0 mM in non-transgenic mice).

The effects of maternal IGFBP-1 over-expression were also studied, and heterozygous pups from homozygous mothers had significantly smaller birth weights compared with heterozygous pups from non-transgenic mothers. Taken together, the authors concluded that the antenatal growth retardation and reduced fetal carbohydrate reserves observed in transgenic mice were related to over-expressed fetal and maternal circulating IGFBP-1. Thus, excess IGFBP-1 may be an important contributing factor in growth retardation and delayed bone development in severe cases of human intrauterine growth retardation.

**Neurobehavioral and quality of life changes associated with growth hormone insufficiency after complicated mild, moderate, or severe traumatic brain injury.**
Kelly DF, McArthur DL, Levin H et al. UCLA School of Medicine, Los Angeles, CA, USA. *J Neurotrauma* 2006;23:928–42.

Editor’s note: During the last 6 years, a number of studies have reported that the frequency of hypothalamic–pituitary dysfunction evident several months or years following moderate to severe traumatic brain injury (TBI) may be as high as 25–40%. The growth hormone (GH) axis appears to be the most vulnerable region to injury, with GH deficiency estimates of 6–25% observed in tested TBI patients. Furthermore, many TBI survivors experience significant morbidity in neurocognitive function and quality of life (QoL) perceptions, and many of these symptoms are very similar to symptoms observed in untreated GH deficient adult
patients. Thus, there is much speculation that the neurocognitive and QoL morbidity observed in TBI survivors may be secondary to underlying undiagnosed GH deficiency.

This prospective study tested the hypothesis that TBI survivors with GH deficiency or GH insufficiency would exhibit greater neurocognitive and QoL impairment compared with those without GH deficiency. Survivors of moderate to severe TBI (median Glasgow Coma Scale=7, n=44) aged 32±18 years were recruited, and studied 6–9 months following head injury using dynamic anterior pituitary function tests (GH axis assessment by growth hormone-releasing hormone plus arginine stimulation), and neurocognitive and QoL tests.

Eight patients (18%) had evidence of GH deficiency or GH insufficiency. With the exception of one patient with evidence of hypogonadism, no other anterior pituitary deficits were detected. Compared with patients that were GH sufficient, the GH deficient and GH insufficient patients exhibited significantly higher rates of depression (p<0.01) and lower QoL scores in perceptions of:

- Physical health (p=0.02).
- Energy and fatigue (p=0.02).
- Pain (p=0.01).
- Emotional well-being (p=0.02).
- General health (p=0.05).

Notably, the GH deficient and GH insufficient patients had similar overall injury characteristics to the 36 GH sufficient patients, although there was a weak, non-significant trend in aggregate computed tomography score that suggests that the GH deficient and GH insufficient groups may have experienced a greater degree of parenchymal brain damage than the GH-sufficient group. Nevertheless, this study supports the hypothesis that GH deficiency itself may be the primary underlying cause of the neurocognitive and QoL deficits observed in the chronic post-TBI period, or is acting in synergy with the residual effects of the brain injury.

C-type natriuretic peptide in growth: a new paradigm.
Olney RC.
Nemours Children's Clinic, Jacksonville, FL, USA.

Editor's note: The present review draws together recent observations in animal models that provide the basis for our understanding of the clinical impact of mutations in the natriuretic peptide receptor-B (NPR-B). In humans, homozygous NPR-B mutations manifest as acromesomelic dysplasia (Maroteaux type). Although this condition is very rare, affecting only 1 in 2 000 000 of the general population, the heterozygous carrier state may be more common and contribute to non-dysmorphic “idiopathic” short stature (J Clin Endocrinol Metab 2006;91:1229–32).

Intravenous insulin-like growth factor-I receptor antisense treatment reduces angiotensin receptor expression and function in spontaneously hypertensive rats.
Nguyen TT, Cao N, Short JL et al.
Monash University, Parkville, VIC, Australia.

Editor's note: Insulin-like growth factor-I (IGF-1) is known to have important effects on the cardiovascular system. In terms of blood pressure modulation, IGF-1 appears to have pressor-inducing effects (vascular smooth muscle cell proliferation) and nitric oxide-dependent vasodilatory effects. Both of these effects are altered in hypertensive animal models. However, there are interactions between IGF-1 and the renin–angiotensin system (RAS) that are associated with vascular resistance and are also thought to be important.

The authors of the present article recently reported IGF-1 receptor (IGF-1R) “knock-down” experiments utilizing a specific IGF-1R antisense oligonucleotide product, that revealed a reduction in pressor responses to angiotensin-II and decreased angiotensin receptor (AT-1R) expression in normotensive rats. The study used a hypertensive animal model.
model to investigate the effects of IGF-1R antisense on AT-1R expression, resting blood pressure, and on blood pressure responses to norepinephrine and angiotensin-II.

Alternate-day intravenous administration of IGF-1R antisense to spontaneously hypertensive rats (SHR) for 2 weeks resulted in significantly reduced IGF-1R expression within aortic and tail arteries when compared with controls (untreated and mismatched treated animals). IGF-1R antisense treatment resulted in reduced AT-1R expression within the vasculature and in reduced pressor responses to both angiotensin-II and norepinephrine. This response to IGF-1R antisense was significantly greater in the SHR group when compared with normotensive rats. IGF-1R antisense treatment had no significant effect on resting blood pressure.

Taken together, these IGF-1R knockdown experiments suggested that inhibition of the local effect of IGF-1 within blood vessels produced a profound effect on vascular responses to vasoconstrictor agents. The large IGF-1R antisense effect observed in the SHR group compared with the normotensive rats. IGF-1R antisense treatment had no significant effect on resting blood pressure.

Genomic imprinting in Turner syndrome: effects on response to growth hormone and on risk of sensorineural hearing loss.


Editor's note: In Turner Syndrome (TS) there is evidence to suggest that an X chromosome parent-of-origin effect exists. For example, phenotypic and neurocognitive profiles appear to differ between those with an intact maternal X chromosome (X\textsuperscript{m}) and those with an intact paternal X chromosome (X\textsuperscript{p}).

In the present study, the authors investigated the parent-of-origin effect of the intact X chromosome on:

- Spontaneous growth.
- Height gain responses to recombinant human growth hormone (rhGH) treatment.
- The frequency of sensorineural deafness.

Subjects aged 10.0±1.7 years (n=54) participating in an ongoing, randomized, control trial of rhGH therapy had parent-of-origin of the intact X chromosome analyses conducted.

In terms of baseline clinical indices, X chromosome parent-of-origin status did not appear to have any bearing on birth weight, birth length, or on the height, age, or bone age at the time of study entry. However, in patients with X\textsuperscript{m}, height standard deviation score before the initiation of rhGH therapy correlated with both mid-parental height (r=0.535; p=0.001) and maternal height (r=0.574; p<0.001), but not with paternal height. When subjected to analysis using a linear regression model, subjects with X\textsuperscript{m} demonstrated a greater mean height gain than those with X\textsuperscript{p}, and 36–53% of the response to rhGH was attributed to X-linked imprinting. Furthermore, X\textsuperscript{m} subjects had a greater mean response to rhGH therapy compared with X\textsuperscript{p} subjects (p=0.017; 95% confidence interval 0.66–6.09). In terms of sensorineural hearing impairment, X\textsuperscript{m} subjects were less likely to have hearing loss compared with X\textsuperscript{p} subjects (p=0.040).

Overall, this study provides further evidence of significant X chromosome imprinting effects on subjects with TS.

A variable degree of intrauterine and postnatal growth retardation in a family with a missense mutation in the insulin-like growth factor I receptor.


Editor’s note: The importance of insulin-like growth factor I (IGF-I) in the regulation of intrauterine development and in post-natal
growth and metabolism is well established. Nevertheless, animal knock-out and other experimental models and gene mutation discoveries in humans continue to provide insights into the key roles played by the various individual components of the IGF-1 system. Human IGF-1 deficiency due to homozygous gene deletion or mutation is characterized by severe intrauterine growth retardation (IUGR), post-natal failure, mental retardation, and deafness. However, the clinical features and phenotype of humans presenting with mutations of type 1 IGF-1 receptor gene (IGF1R) are less well defined.

The present authors described a mother and daughter from the same family (aged 35 years and approximately 16 months, respectively) with a novel heterozygous mutation of the IGF1R gene (G3148>A substitution). This missense mutation is associated with IUGR and post-natal growth retardation, and is located in the intracellular tyrosine kinase domain of the IGF1R gene. The mutation results in a partial resistance to IGF-1, which has been confirmed by in vitro studies that demonstrated normal IGF-1 binding to the receptor, but reduced activation of the downstream signaling cascades.

The phenotypes of the mother and daughter were similar to the few (n=8) previously reported cases of mutations of IGF1R, with respect to:

- Degree of IUGR (maternal birth-weight standard deviation score [SDS] = −2.1, child SDS = −3.3).
- Reduced post-natal growth (maternal height SDS = −4.0, child height SDS = −2.3).
- Head circumference (maternal SDS = −3.0, child SDS = −5.6 SDS).

By comparison with the previous reports, which described mutations affecting the extracellular domain of IGF1R, the authors highlight the high degree of variability that appears to be evident within and between the IGF1R mutation categories in:

- Mental performance (reduced in mother, normal in child).
- Dysmorphic features (absent in mother, present in child).
- Birth length (−0.3 SDS in mother, −4.2 SDS in child).

The authors speculated that this heterogeneity in phenotype might reflect the degree of remaining IGF-1 signaling within tissues. Furthermore, they hypothesized that the presence or absence of maternal IGF-1 resistance may partially determine birth weight, and might explain the variance in IUGR evident in those offspring that are also heterozygotes for the IGF1R mutation.

**GH secretory pattern in young adults who discontinued GH treatment for GH deficiency and decreased longitudinal growth in childhood.**

Svensson J, Johannsson G, Iranmanesh A et al. Sahlgrenska University Hospital, Goteborg, Sweden.


Editor’s note: It is well established that some patients diagnosed with growth hormone (GH) deficiency during childhood no longer appear to be GH deficient when retested at completion of linear growth in mid to late adolescence. The vast majority of the patients falling into this category appear to have been diagnosed with so-called idiopathic GH deficiency, with no obvious structural abnormalities or pathology of the hypothalamic–pituitary structures to account for their GH deficient status. It is suspected, but not yet confirmed, that these patients may have a neuroendocrine defect in the spontaneous pattern of GH release.

The present authors conducted a study in which 24-h GH profiles were performed in a group of 37 adolescent (mean age 19 years) diagnosed with poor growth velocity secondary to GH deficiency during childhood. Subjects were grouped according to whether retesting in late adolescence revealed persisting GH deficiency (GH deficiency n=19, of whom 10 had an organic cause of GH deficiency) or GH
sufficiency (n=18, of whom 17 had previously been diagnosed with “idiopathic” GH deficiency). GH profiles were assessed 1 year following discontinuation of recombinant human GH (rhGH) therapy, and were compared with the GH profiles of 16 age-matched healthy controls.

Assessment of GH secretion patterns (using deconvolution analysis) in the GH deficiency group revealed significantly lower basal, pulsatile, and total GH secretion rates, with increased frequency of GH pulses, but lower mean pulse area when compared with healthy controls. In contrast, adolescents in the GH sufficiency group had a pattern of 24-h GH secretion that was similar to controls.

Whilst this study distinguishes patterns of GH secretion in adolescents and young adults following discontinuation of rhGH therapy initiated for apparent GH deficiency in childhood, it cannot explain why those subsequently found to be GH sufficient (almost exclusively those with a previous diagnosis of idiopathic GH deficiency) had evidence of inappropriate GH secretion and poor growth velocity in childhood.

Insulinlike growth factor I affects ocular development: a study of untreated and treated patients with Laron syndrome.
Bourla DH, Laron Z, Snir M et al.
University of California, Los Angeles, CA, USA

Editor’s note: In brief, Laron syndrome (LS) is a dwarfism that is associated with low serum levels of insulin-like growth factor 1 (IGF-1), despite subjects having elevated growth hormone (GH) levels.

It has been reported by previous studies that there is a relationship between decreased ocular pathological features in children with GH deficiency and LS.

In this study, the authors investigated the relationship between ocular dimensions and LS, and the effect of IGF-1 on ocular growth in LS patients. In order to evaluate this, the authors recruited 12 patients with LS, 8 of whom were untreated (LS group; average age 46 years) and 4 who were treated with IGF-1 (LS-T group; average age 15.2 years), and 30 control patients (average age 45.2 years). All patients were subjected to a full ophthalmic examination, which included, for example, best-corrected Snellen visual acuity, automated corneal keratometry and refractometry, and ultrasound biometry.

Their results showed that the average axial length (AXL) of eyes of the LS group was significantly lower (p<0.01) compared...
with AXL for the control group. The LS-T group also had a higher average AXL compared with LS patients; however, this was not statistically significant. The average chamber depth (ACD) was found to be 2.55, 3.48, and 3.84 mm in the LS, LS-T, and control groups, respectively, showing a significant statistical difference only between the LS and LS-T groups (p<0.001). Average lens thickness for each group was 4.56 mm in the LS patients, 3.77 mm in the LS-T patients, and 3.51 mm for the control patients, showing a significant statistical difference between the LS and LS-T groups and also between the LS and control groups (p<0.001). Furthermore, there was a statistically significant difference of average corneal curvature between the LS and LS-T groups versus the control groups (p<0.001).

Overall, the results indicate that LS patients treated with IGF-1 had better ocular growth compared with LS patients who weren’t treated with IGF-1, although this was not mirrored when IGF-1-treated LS patients were compared with healthy controls.

In conclusion, the authors found that IGF-1 was important in regulating ocular growth in LS patients, although the mechanisms involved in this have not yet been fully elucidated. The latter should be more fully investigated in further studies.

**Growth hormone promotes skeletal muscle cell fusion independent of insulin-like growth factor 1 up-regulation.**

Sotiropoulos A, Ohanna M, Kedzia X et al.
Institut National de la Santé et de la Recherche Médicale, Paris, France.

Editor’s note: Although postnatal growth of skeletal muscle is coordinated by growth hormone (GH), the underlying mechanism of this process has not been fully described.

The present study used a growth hormone receptor (GHR)-minus (GHR−/−) mouse model to investigate the way in which skeletal muscle responds to GH. A disproportionate reduction in muscle mass was observed in GHR−/− mice compared with control mice, and the myofiber cross-sectional areas of mutant mice were 36–40% smaller than those of wild-type (WT) mice. However, the number of myofibers present in muscle was the same for the two groups. This indicated that GHR deletion does not affect myofiber formation during embryogenesis, but does inhibit postnatal myofiber growth. Furthermore, the differentiation of muscle into oxidative type 1 myofibers and glycolytic type 2 myofibers was affected. In GHR−/− mice, a 26% decrease in type 1 fiber number and a 16% increase in type 2 fiber number was observed in soleus muscle. An increase in hybrid fibers was also found. The authors concluded that GH has a positive affect on type 1 fiber specification.

Further investigation, using WT and GHR−/− murine cell cultures, showed that myotubule size was controlled in a cell-autonomous manner by GH, and GHR−/− cells formed myotubules that were 25% smaller than those in WT cells. Conversely, GH stimulation of WT cells increased myotube size by 20%. These size differences were comparable at 48, 72, and 96 h after transferring cells to mitogen-poor differentiation medium (DM), indicating that GH controls myotubule size during early differentiation. However, GH had no effect on myoblast precursor cell size, proliferation, or differentiation. Nascent myotubes are formed by myoblast–myoblast fusion, and rapid growth occurs when myoblasts subsequently fuse with myotubes. After 48 h in DM there was no difference in the number of fused cells (as a proportion of total cell number) in WT and GHR−/− cultures, indicating that myotube formation was not controlled by GHR signaling. However, GHR−/− myotubes had fewer nuclei compared with WT myotubes. Therefore, the authors suggested that GH may increase muscle cell size by recruiting new nuclei to existing myotubules.

Insulin-like growth factor 1 (IGF-1) gene expression did not correlate with GHR activation or with GH mediation of myotube size. This finding, when looked at in the context of previous studies, indicates that local IGF-1 upregulation does not mediate
the GH-controlled skeletal muscle fusion and size.

Further investigation into the influence of GH on myotube size may have implications for stem cell transfer therapies and future treatment of muscle disorders, including Duchenne muscular dystrophy. However, the present article reinforces the message that the control of cell growth is not simply a matter of switching a single gene on and off.

**Insulin-Like Growth Factor-I and Growth in Height, Leg Length, and Trunk Length between Ages 5 and 10 Years.**

Editor’s note: Insulin-like growth factor 1 (IGF-1) being the growth hormone (GH) mediator, is supposed to be responsible for the final adult height. As height consists of both trunk and leg length, and in the prepubertal period a greater proportion of growth in total height results from growth in leg rather than trunk length, this study was conducted with the hypothesis that adult leg length may be a marker for IGF-1 levels during childhood. Serum IGF-1 levels were measured in healthy prepubertal children, and subsequently related to growth in height, leg length, and trunk length.

The study was carried out in >14 000 pregnancies over a 20 month period. Anthropometric data and blood were collected for analysis at ages 5, 7–8, and 9–10 years of age. The study comprised 1260 children. It was observed that at age 5, IGF-1 levels correlated positively with total height, and leg and trunk length in both boys and girls. The relationship was not much better in leg length compared with trunk length in either boys (p=0.3) or girls (p=0.8). Total growth in height and trunk length was positively associated with IGF-1 in both sexes at 8 years of age. Boys, in particular, had a strong association between IGF-1 and growth in leg and trunk length; however, there were no data suggesting that IGF-1 was more strongly associated with one particular growth component (p=0.34 for adjusted analysis). On the other hand, girls were found to have a strong positive association between IGF-1 and growth in trunk length, but the results did not show any association between IGF-1 and growth in length. No relationship was found between IGF binding protein-3 and height growth between girls and boys (p interaction= 0.21).

This study found relationships between final height and childhood IGF-1 levels, thus suggesting that final adult height may be a marker for childhood IGF-1. Now, the question arises of whether levels of IGF-1 can be used as the final height outcome and initiation of GH or IGF-1 supplement therapy.

**Stature in children with chronic kidney disease: analysis of NAPRTCS database.**
Seikaly MG, Salhab N, Gipson D et al.
University of Texas Southwestern Medical Center, Dallas, TX, USA.

Editor’s note: Children with chronic kidney disease experience poor growth of multifactorial etiology. Nutritional, metabolic, and hormonal factors are implicated and the use of recombinant human growth hormone has been shown to improve growth.

Seikaly et al. analyzed the NAPRTCS (North American Pediatric Renal Transplant Cooperative Studies) database, which included >5000 children, in order to determine the relationship between height and a variety of parameters. Factors associated with being short at entry to the database included younger age, lower glomerular filtration rate, and anemia, while black patients and those with focal segmental glomerulosclerosis were at a lower risk. Data of this type are of limited practical value and it is clear that growth failure continues to be a significant problem despite advances in medical treatment. Traditional risk factors, including acidosis, calcium, phosphate, albumin, and parathyroid hormone levels, were poor independent predictors of short stature.
**GH Deficiency**

**Pituitary stalk compression by the dorsum sellae: possible cause for late childhood onset growth disorders.**
Taoka T, Iwasaki S, Okamoto S et al.
Nara Medical University, Nara, Japan.

Editor’s note: The anatomical and physiological bases for childhood-onset growth hormone (GH) deficiency remain unclear. Perinatal traumatic events (such as breech delivery) and genetic disorders associated with hypothalamo–pituitary embryological transcription factors are established causes of a variety of pituitary hormone deficiency syndromes. However, there remains a large unexplained cohort of GH deficiency and other pituitary hormone deficiencies.

This study of 34 GH deficient, short-stature children and 24 age-matched normal stature children examined the magnetic resonance imaging appearances of the pituitary and pituitary stalk. The pituitary stalk appeared to be compressed against the dorsum sellae and distorted in nine of the GH deficient children, indicating that this anatomical relationship might be causally related to functional GH deficiency. Conversely, GH deficiency might be responsible for the pituitary stalk–dorsum sellae deformity. The posterior pituitary lobe had normal signal intensity and localization in all patients. Interestingly, pituitary stalk compression was significantly correlated with onset of GH deficiency in children ≥7 years old, and was rarely found in children <6 years. The authors suggest that this may be due to the slow growth rate of the dorsum sellae, which only becomes large enough to compress the pituitary stalk during late childhood.

Although there is no apparent explanation (from medical history) for the sequence of developmental events that led to this anatomical and, presumed, functional abnormality, it is reasonable to accept that compression and distortion of the pituitary stalk is an associated cause in late-onset cases of functional GH deficiency. Future follow-up studies are indicated to determine whether or not the pituitary stalk–dorsum sellae relationship changes over time, possibly with evolution of multiple pituitary hormone deficiencies.

**Adult heights in patients with permanent growth hormone deficiency with and without multiple pituitary hormone deficiencies.**
Maghnie M, Ambrosini L, Cappa M et al.
University of Genoa, Genoa, Italy.

Editor’s note: The present retrospective study evaluated factors contributing to differences in final height in patients with isolated growth hormone deficiency (IGHD) compared with final height in those with multiple pituitary hormone deficiencies (MPHD).

Five treatment centers contributed to the study and recruited patients with IGHD (n=39) and with MPHD (n=49) who had been diagnosed at mean ages of 7.7 years and 6.9 years, respectively. Re-evaluation of GH status was performed at a median age of 17.6 years (IGHD) and 19.8 years (MPHD) to confirm that GH deficiency was present. GH deficiency was confirmed if GH peak levels were <3 μg/L after an insulin tolerance test or failed to rise >10 μg/L following provocative tests. Fifteen subjects were designated as having idiopathic IGHD on the basis of a normal magnetic resonance image (MRI) of the pituitary, with 73 patients showing congenital hypothalamopituitary abnormalities. Five treatment centers contributed to this study.

Median height at onset or induction of puberty was similar for the IGHD and MPHD patients, although puberty onset for both sexes was 1 year later in the MPHD group than in the IGHD group. Pubertal height gain was similar for the two groups, with median final heights of 168 and 170 cm for IGHD and MPHD males, respectively, and 160 and
157 cm for IGHD and MPHD females, respectively. The median GH treatment dose was approximately 0.2 mg/kg/week for both groups, although a variety of dosage schedules (3–7 doses per week) were used during the overlapping treatment periods for these patients. A few patients had received pituitary-derived human GH prior to the availability of recombinant GH.

The authors suggested that the greater final height of patients with MPHD was due to the late onset of puberty in this group of patients, compared with patients with IGHD. They therefore argued that introducing sex steroid replacements might be beneficial in patients with MPHD, and not seriously detrimental to final height attainment. A marginal height gain through delayed induction of puberty may indeed be less important to the long-term well-being of the hypogonadal patient. However, the absence of relevant psychological studies of adolescents with MPHD limits the complete understanding of the optimal management pathways.

**Endocrine dysfunction and parameters of the metabolic syndrome after bone marrow transplantation during childhood and adolescence.**

Shalitin S, Phillip M, Stein J et al. Schneider Children’s Medical Center of Israel, Petach Tikva, Israel.

*Bone Marrow Transplant* 2006;37:1109–17.

Editor’s note: The present authors produced a comprehensive account of multiple endocrine disorders that arose during long-term follow-up of 91 patients after bone marrow transplantations (BMTs). The mean age at diagnosis was 5.6 years (0.1–18.5) and patients were aged 4–32 years at follow-up. Indications for transplant were:

- Hematological malignancies (44.2%).
- Solid malignant tumors (28.8%).
- Other systemic disorders (26.9%).

Following primary surgical or other therapy, 66% received chemotherapy alone, 11% received chemotherapy and radiotherapy, and only 23% were treated with BMT alone. The mean age at BMT was 7.3 years (range 0.6–21.5 years) and the mean duration of follow-up after BMT was 6.2 years (range 1–22.5 years).

Endocrine side-effects were observed in a significant number of patients and were associated with cranial irradiation and total body irradiation. Of the BMT patients, 10 developed growth hormone deficiency, 12 developed primary hypothyroidism, and one developed papillary thyroid carcinoma. Furthermore, 24 patients (54% of girls aged ≥13 years and 29% of boys aged ≥14 years) developed primary gonadal failure by the time of final evaluation. Gonadal failure was more frequent in:

- Patients who had BMT to treat hematological disease.
- Patients treated with radiotherapy.
- Patients of advanced pubertal age at BMT.

Further concerns for the long-term health of childhood cancer survivors included evidence at follow-up of type 2 diabetes and other adult metabolic syndrome parameters. Obesity was present in 4.4%, type 2 diabetes in 3.3%, impaired glucose tolerance in 3.3%, and dyslipidemia in 28% of the 43 patients tested.

The authors acknowledge important limitations in their study, including the small size of the cohort, and the small number of patients who had reached final adult height and had entered puberty by the end of the study. Careful long-term follow-up in an appropriate clinical setting is clearly essential for the growing number of childhood cancer survivors.

**GH replacement does not increase the risk of recurrence in patients with craniopharyngioma.**


*Clinical Endocrinology* 2006;64:556–60.

Editor’s note: Craniopharyngioma is one of most common primary intracranial tumors.
in children. Although histologically a benign tumor, the craniopharyngioma is known for its recurrence potential even after apparent successful therapy. The recurrence is associated with significant morbidity and mortality rates.

Endocrine abnormalities, especially growth hormone (GH) deficiency, are commonly associated with craniopharyngioma. The hormone deficiency is attributed to multiple factors including tumor mass effect, recurrence and/or consequence of therapy of the tumor itself. GH replacement has been beneficial in these patients, and GH therapy has been implicated in possible recurrence and tumor growth through its direct action or indirect action via insulin-like growth factor-1 (IGF-1).

In this retrospective study, the authors assessed the effects of GH replacement on tumor recurrence. The study included all patients with craniopharyngioma who reported at their institution for over 40 years. The treatment included surgical resection (gross total removal [GTR], partial removal [PR]), and surgery with radiotherapy (S+RT). The GH deficiency was diagnosed with auxiological data in children and GH stimulation tests in children and adults. The recurrence of tumor was diagnosed by residual tumor in GTR, and tumor growth in PR. Computed tomography scans and magnetic resonance imaging were used after 1980 and 1990, respectively, to visualize the tumor recurrence.

Of a total of 94 subjects, 41 received GH replacement therapy, nine patients did not have follow-up imaging studies. Tumor recurrence was observed in 4 patients who were treated with GH and had a mean follow up of 0.7–6.8 years of therapy, and 22 non-GH treated subjects had tumor recurrence with 0.9–11 years of follow up. The analysis showed that GH therapy was not a significant independent predictor of tumor recurrence. This study of approximately 20 years of therapy and long-term data from Genentech’s National Cooperative Growth Study (approximately 15 years), which showed a recurrence rate of 6.4% in children who were treated with GH. In fact this is lower than the general pediatric population with craniopharyngioma. The data available so far are from retrospective studies; it is unlikely to have prospective long-term studies, as monitoring for recurrence is easily carried out using the imaging studies while patients are treated with GH therapy for ultimate growth in children, and quality of life and cardiovascular morbidity and mortality benefits in adults.

Effects of growth hormone substitution therapy on cognitive functioning in growth hormone deficient patients: a functional MRI study.
Arwert LI, Veltman DJ, Deijen JB et al.
VU University Medical Center, Amsterdam, The Netherlands.
Neuroendocrinology 2006;83:12–9.

Editor’s note: The identification of growth hormone (GH) receptors in the brain, and subsequent demonstration of improved cognitive function in adult GH-deficient patients receiving GH replacement has focused research towards establishing causally related mechanisms.

This small, but significant, double-blind study examined 13 childhood-onset GH-deficient patients who were recruited at a mean age of 27±7 years following a 3-month washout period without GH treatment. Following washout, five patients received active GH treatment and seven patients received a placebo. One patient dropped out of the study due to protocol violation. All patients were confirmed GH deficient prior to the study by repeat testing and had low serum insulin-like growth factor-1 (IGF-1) levels. Serum IGF-1 levels were monitored during GH treatment to verify the adequacy of GH replacement. Cognitive assessments were taken at baseline and after 6 months of GH treatment or placebo, together with functional magnetic resonance imaging (fMRI).

There was a highly significant improvement in both long-term and working memory function in the GH-treated group compared with the placebo group (p=0.004). This improvement was associated with

Effects of growth hormone substitution therapy on cognitive functioning in growth hormone deficient patients: a functional MRI study.
fMRI activations during working memory tasks of prefrontal, parietal, motor, and occipital cortices, as well as in the right thalamus and anterior cingulated cortex. A further interesting observation was the decreased activation in the ventrolateral prefrontal cortex in GH-treated patients compared with control patients. The authors suggested that this difference indicated decreased effort and more efficient recruitment of the neural systems.

The preliminary data from this study are interesting and merit more extensive studies on patients with a spectrum of childhood and adult-onset causes of GH deficiency, using cross-over groups and sequential studies of treatment and withdrawal of GH.

Peripheral fibrinolytic markers, soluble adhesion molecules, inflammatory cytokines and endothelial function in hypopituitary adults with growth hormone deficiency.


Editor's note: Growth hormone (GH) replacement in GH-deficient adults has been associated with reduced mortality risk. The factors responsible for this have not yet been adequately identified, and are not necessarily related to simple cardiovascular risk factors and related mortality events.

In this study, 10 patients with GH deficiency (50% male) were studied at baseline and at 1 year following initiation of GH replacement therapy. With a mean age of 46±10 years, these patients were compared with nine male and 16 female controls, matched for body mass index and age. All were lifelong non-smokers, normotensive, and non-diabetic. A number of variables were recorded, including fibrinolytic markers, soluble adhesion molecules, inflammatory cytokines, and endothelial functions.

Compared with controls, baseline observations showed that GH deficient patients had higher:

- Hip–waist ratios.
- Body fat levels.
- Fasting insulin concentrations.
- C-peptide concentrations.
- E-selectin concentrations (2.5-fold).
- Triglyceride concentrations.

However, after 1 year of GH treatment there were no changes in biochemical parameters, fibrinolytic markers, soluble adhesion molecules, inflammatory cytokines or endothelial function. Clearly more extensive studies are required to define the GH dependent factors or other life-style issues that place the GH deficient adult at increased mortality risk, within or without the context of GH deficiency itself.

Pathophysiology of radiation-induced growth hormone deficiency: efficacy and safety of GH replacement.


Editor's note: This is an excellent review of the pathophysiology of radiation induced growth hormone (GH) deficiency, GH therapy, and safety. The review is summarized below.

Radiotherapy has been used for various childhood malignancies, including hematological cancers, and brain and skull based tumors. Treatment may involve brain and/or spinal radiation, and whole body irradiation, which can damage the hypothalamus and result in hypothalamic–pituitary dysfunctions. Within the hypothalamic–pituitary axis (HPA), the somatotropic axis is the most radiosensitive. Studies in rats have shown that a radiation dose as little as 3 Gy can damage the somatotrophs and inhibit the production of GH, whereas it took 10 Gy to inhibit thyroid-stimulating hormone (TSH)-producing cells. It follows that GH deficiency is the commonest neuroendocrine injury following cranial irradiation for non-pituitary brain...
tumors, with almost all children treated with >30 Gy showing defective GH responses to the insulin tolerance test. These radiation-induced hormone deficiencies are time-dependant – both the incidence and severity of disorders increase with time after radiation. They have also been shown to be related to the dose and site of radiation.

Growth deficiencies in cancer patients are often attributed to radiation-induced GH deficiency. However, there are many other factors associated with cancer and its treatment that can influence growth. Growth impairment in children treated for brain tumors during the first year seems unrelated to GH deficiency, unlike growth impairment seen in hematological malignancy patients. Spinal irradiation seems to be responsible for growth deficiencies in the first few years after radiation therapy, but GH deficiency does become important in later years.

Response to short-term GH therapy in radiation-induced short stature has been encouraging. However, in the long term it has not been able to produce the catch-up growth seen in those with idiopathic short stature. It has, however, been shown to maintain height percentile into adulthood, whereas patients not treated with GH therapy continue to decrease in height percentile. In recent studies, height loss has been much lower, as the dose of GH has been adjusted to age and weight, as well as the use of gonadotropin-releasing hormone (GnRH) analogues to delay the epiphyseal closure and give an extra window for prolonged GH therapy.

The children who had pharmacological evidence of GH deficiency have the worst final height of up to 1.7±0.2 standard deviation scores compared with 0.9±0.2 in children with normal peak GH response. This suggests that final height can be achieved by instituting GH therapy at an earlier stage in these subjects.

There are some safety concerns associated with GH therapy due to the risks of new or recurrent tumors and malignancies. Various data, especially from the National Cooperative Growth Study of Genentech, so far has suggested that the risk of a second or recurrent malignancy is in fact lower than the normal population.

GH therapy is safe in patients with radiation-induced GH deficiency in both the final height outcome in children and quality of life in adults, and it is efficacious compared with patients who are not treated, as the risks of recurrence or new tumor formation are no more than in the normal population.

**Healthcare utilization, quality of life and patient-reported outcomes during two years of GH replacement therapy in GH-deficient adults – comparison between Sweden, The Netherlands and Germany.**

Saller B, Mattsson AF, Kann PH et al.
Pfizer GmbH, Karlsruhe, Germany.

Editor’s note: The present study used information derived from the Kabi International Metabolic Study (KIMS) database to determine changes in healthcare utilization and quality of life (QoL) in adults receiving growth hormone (GH) replacement therapy.

QoL assessments were conducted with 302 Swedish, 103 Dutch, and 98 German patients at baseline, and after 1 and 2 years of GH replacement. Analysis was made of the QoL-Assessment in GH-Deficient Adults (QoL-AGHDA) questionnaire and the KIMS patient Life Situation Form to evaluate healthcare utilization. The cohorts from the three countries were demographically similar, with a mean age at enrolment of approximately 50±13 years and a mean body mass index of 27. Approximately 50% of the patients were male.

The cause of GH deficiency in most patients was pituitary adenoma (60–65%), and other causes included craniopharyngioma (7–15%). Isolated GH deficiency (IGHD) was present in 4–15%, and approximately 90% of patients from each country had adult-onset GH deficiency. Approximately 70% of patients had undergone pituitary surgery, and time between surgery and study onset varied from 0–20 years. The parameter showing the greatest variation between the three countries
was the use of cranial radiotherapy, with 55% of Dutch patients, 37% of Swedish patients, and just 7% of German patients experiencing radiotherapy.

Patients from the three countries showed very similar responses to the QoL assessments before and following GH treatment. Improvement in QoL was apparent after 1 year, and was sustained at 2 years by approximately 3 points on the QoL-AGHDA scoring system. The improvement in QoL was associated with a restoration to normal or above average serum insulin-like growth factor 1 levels in both sexes, and a reduction in recorded number of days of sick leave (significant at 63%) compared with pre-treatment status.

These data highlight the importance of evaluating the benefit of GH treatment in the context of daily living experiences. Furthermore, alternative ways of assessing the contribution to society of the GH-treated adult, through active gainful employment and reduced demand on the healthcare services, might support the argument for extended GH replacement through adult life.

The effects of growth hormone (GH) deficiency and GH replacement on cognitive performance in adults: a meta-analysis of the current literature.
Falleti MG, Maruff P, Burman P et al.
CogState Ltd, Melbourne, Australia.

Editor’s note: Although the many beneficial effects of growth hormone (GH) replacement therapy are well known, there is growing evidence to suggest it is important for the normal functioning of the central nervous system (CNS). At present, most conclusions about the existing relationship between GH deficiency and cognitive function have been based on cross-sectional comparisons between GH deficient patients and healthy controls. The reliability of such studies is questionable in regards to several methodological issues (i.e. performance of GH patients is matched to healthy controls). Such issues may reflect secondary consequences of GH deficiency rather than primary CNS-related consequences. The present study sought to improve the understanding of the nature and magnitude of cognitive impairment in GH-deficient patients. This was achieved by performing a meta-analysis of the existing literature, comparing the performance of patients with GH deficiency and GH treated patients with controls, baseline and treatment comparisons, and the measurement of size of treatment effect.

The authors identified 13 studies that met the inclusion criteria, with a total of 64 neuropsychological tests measures used.

GH deficiency showed a moderate-to-large impairment of cognition, with a slightly larger effect on language compared with other domains. In addition, GH treated patients showed impairments in cognitive function (particularly memory function) when compared with controls.

Overall, following analysis, the authors conclude that patients with GH deficiency can achieve improvements in cognitive function with GH replacement therapy.

Surgery

Gamma knife radiosurgery for acromegaly – long-term experience.
Jezková J, Marek J, Hána V et al.
Charles University, Prague, Czech Republic.
Clinical Endocrinology 2006;64:588-95.

Editors note: Neurosurgery and pharmacotherapy are well-established first-line treatments of patients with acromegaly. The success of neurosurgery depends on the size of pituitary adenoma and experience of surgeon. The successful surgery varies between 80-90% of microadenoma and up to 50% of macroadenoma removal. The remainder of patients with residual and functional tumor may require long-term
pharmacotherapy, radiotherapy, or a combination of both, and rarely re-surgery. Primary pharmacotherapy has its own limitation, such as need of life long treatment, cost, and variable success on hormone secretion and tumor size.

Conventional radiotherapy has slow onset, the hormonal normalization is not achieved ≥10 years after radiotherapy. There are increased side effects of conventional irradiation locally.

The use of gamma knife radiosurgery for acromagaly is very recent, and long-term data are scarce. In this study, the authors studied 96 patients with Leksell gamma knife (LGK) treatment and followed up to 120 months. The patients included 46 women, aged 16–76 years. Of the 96 patients, 71 had undergone surgery before LGK treatment, and 11 of these patients had conventional irradiation prior to LKG. Twenty-four patients were treated primarily with LKG irradiation. The patients were followed at different times using hormonal analysis, and magnetic resonance imaging scans.

The results of the current study provide a very positive outlook on the long-term effectiveness of LGK therapy for acromagaly without any adverse effects, including absence of peri-pituitary gland. LGK therapy should be considered as a therapeutic tool after neurosurgery in patients with residual tumor, as long-term cost may be less with LGK compared with pharmacological treatment. LGK therapy should be considered as a primary therapy in patients who are not surgical candidates or who do not want long-term medical therapy.